for small quantities in the blood stream, have to date been unsuccessful, a most interesting observation in the light of the vegetative theory of the nervous system control of the processes of pigmentation.

Addison's disease is, of course, the classic example of pigmentation following glandular insufficiency. However, in not all of the cases can actual histologic changes be detected in the adrenals. In a few cases the lesions are in other parts of the chromaffin system, such as the paraganglia and sympathetic ganglia, all derivatives of the sympathetic nervous system. Cases are reported following destructive lesions of these autonomic nervous-system structures, caused by carcinomatous invasion, tuberculosis, syphilis and bacterial infections and drugs, particularly the arsphenamins.

The supposition is that these patients have a congenital insufficiency of their chromaffin system which makes it more susceptible to injury. Whether this hypothesis is true or not, certain it is that interference with the secretory nervous supply of the suprarenal will result in melanotic pigmentation of the skin and mucous membranes.

Epinephrin, a product of the chromaffin tissues, seems to be in some integral way connected with the deposit of melanin in the skin. We know that epinephrin is closely related to tyrosin, a chromogenic substance, capable of producing pigments. The supposition is that, if the adrenal is functioning normally, the tyrosin is converted into epinephrin; but in case of hypofunction of the suprarenals, the tyrosin is unable to break down any further, and this may result in pigmentation.

Just a word as to the local processes of pigmentation. The hyperpigmentation, resulting from disturbances of the endocrine system, arising from lesions within the glands themselves, or, secondarily to interference with their autonomic nervous supply, appears to be merely a quantitative increase in the normal processes of pigmentation. The activity of the melanoblasts is greatly increased. Many more cells participate in the action, and the basal layer histologically appears a black band from which many dendrites ascend. However, the fundamental process of melanogenesis appears to be unchangeed.

RESULTS OF TREATMENT OF CONGENITAL LUETICS WITH BISMUTH ARSPHENAMINE SULFONATE (BISMARSEN) FOR FIVE YEARS*

By WILLIAM ANTHONY REILLY, M.D.
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DISCUSSION *by Hartzell H. Ray, M.D., San Mateo; Merlin T.-R. Maynard, M.D., San Jose; Stanley O. Chambers, M.D., Los Angeles.*

BISMUTH arsphenamin sulfonate, hereafter referred to by the trade-name "Bismarsen," has distinct advantages for the treatment of children suffering from congenital lues. It is given intramuscularly with less effort for the physician, and discomfort for the patient, than is an intravenous antisyphilitic drug. The local and general reactions are much less frequent and severe. The toxicity is less than from such common antisyphilitics as sulpharsphenamin, neoarsphenamin or mercurials, and the therapeutic effectiveness is very high. This means that children will be more faithful to therapy and good results can be achieved. Stokes and Raiziss[1] (the latter the originator), and Chambers,[2] have reviewed the chemical constitution and pharmacological properties of the drug.

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CLINICAL MATERIAL FOR THIS STUDY

The use of Bismarsen was initiated in our Pediatric Clinic in 1930, as part of a coöperative study with Chambers. Many acquired cases in adults have been treated with this drug, but few cases of congenital luetics have been reported. Chambers and Koetter[3] observed a group of 180 children for from one and a half to two years, who had received over 6,000 injections, which is the largest and most comprehensive study. Our group comprises 170 children ranging in age from birth to sixteen years, observed for five years and having had over 3,200 injections. Our technique differed from that of Chambers and Koetter, since we were able to treat these patients only once a week, while their patients were treated twice weekly.

RESULTS

Reactions.—Reactions occurred twenty-six times, or less than 0.8 per cent, and twenty-two, or 90 per cent of the reactions were immediate, eighteen being nitritoid only and four also having purpura. The purpuras occurred twice in two patients, and in the only examination done, there was not a reduced platelet count. The nitritoid reactions were not very severe and were readily controlled by epinephrin. The Zarisch-Herxheimer reaction occurred once, two years after the patient started treatment with this drug. No reactions from bismuth were encountered. The infrequency of reactions, and their relative mildness, are two of the advantages of the use of the drug.

Toxicity.—The 12 to 15 per cent of arsenic in the arsphenamin and the 25 per cent of bismuth in the compound, make it necessary to watch for skin, liver, kidney, blood and peripheral nerve effects. Such were extremely uncommon. Two patients had a very mild albuminuric nephritis, which rapidly cleared. The reactions noted above might be added as toxic manifestations, especially the purpuras in two patients. One patient was desensitized successfully without a recurrence of the purpura. There were no instances of arsenical anemia, dermatitis, neuritis, or enteritis. This also applies to the less frequently encountered bismuth poisoning. The rarity of toxicity is another advantage of this drug.

Effects on Lesions.—Congenital lues in this locality is usually latent and tertiary, due to the widespread treatment of pregnant mothers. The clinical signs and symptoms are few (about 16 per cent of patients), and the diagnosis depends mainly on the serology.

Infants with secondary manifestations of a very active nature are usually difficult to treat with any drug. Bismarsen seemed to be less toxic to them, if given in very cautious doses beginning with 10 milligrams, and apparently controlled the dissemination of the spirochete very well. Only two such cases were fatal in a group of ten. Table 1 shows the favorable reactions the drug has on the lesions at all ages. Skeletal lesions healed rapidly and well, except in fatal cases. This applies in a lesser degree to skin and mucosal lesions. One infant with snuffles was very slow to heal, and required about two months. Eye lesions, mainly

TABLE 1.—*Twenty-four Patients Having Lesions*

Systems	Skeleton	Eyes	Skin	General Condition, Anemia, Nutrition, etc.
Number	7	6	7	10
Per cent cured or helped	85	70	72	70

interstitial keratitis, required, as is usual, about two months of therapy for good results. Bismarsen is rather slow in this condition. In general, patients, especially infants, responded very well despite the low figure. The drug has often proved a life-saver to infants suffering from very active lues. Two infants died, and one had a slowly advancing malnutrition, when the family stopped treatment.

Bismarsen is quite as satisfactory in controlling clinical lesions as are other drugs. In believe it is superior to neoarsphenamin, which is often too toxic for infants with florid syphilitic lesions.

Effects on Blood Serology—There was adequate check-up of blood serology on sixty-one patients, and this, on the whole, showed a very good percentage of reversal, or marked improvement—85 per cent.

If the reversal to negative and the less positive reactions are grouped, the percentage of patients who were improved is 85 per cent. If only the negative serology is considered, the percentage is 61 per cent. As will be noted later, very few have had a relapse to positive serology. It must be recalled that many of the patients with positive serology will eventually become negative. This is even true in children who start therapy after the fifth or tenth year, and more true if therapy is started in early infancy. This experience is quite parallel with many other drugs used for congenital lues.

It is notable that nearly 100 per cent of the infants are blood curable with Bismarsen. They averaged two courses covering about one year of time.

Children between two and five years of age were also almost 100 per cent blood curable, and required about two courses. The proportion of blood reversiblity is around 50 per cent for children starting therapy between five and fourteen years of age. Here the latent tertiary condition of congenital lues resisted with Wassermann fastness, and often three to six courses of from one and a half to three years of persistent treatment were required. Regular therapy was more important than the number of injections, although, if it were practical, better results might have been achieved with treatments twice weekly rather than once a week.

Effects on Spinal Fluid Serology.—Thirteen patients, of a group of forty-three that had spinal fluid examination, showed evidence of central nervous system lues. Another group of fourteen, not so examined, had very suspicious evidence. This is a rather high incidence; at least 30 per cent of the children examined had nervous system involvement. Only three patients have been rechecked after therapy, and fluids were reversed to normal findings; one, an infant, after twelve treatments during two and a half months, has had no recurrence in four years; the second, a fourteen-year-old boy, after 114 treatments in three and a half years, and the third, a girl of seven years who had only one year of treatment. The other patients were either unable to continue treatment with this drug, for various reasons, or have not been rechecked by spinal puncture.

Direct appraisal of its effects on central nervous system lues cannot be given, but certain generalities seem to be definitely known. Bismarsen has caused reversal of blood serology in four other patients, where reëxamination of the spinal fluid could not be done. There was also very definite improvement in the personality and behavior problems, which are so characteristic of many congenital luetics, in two of our patients. We have seen the drug act as a life-saver in two infants with positive spinal fluid. Furthermore, nervous system

TABLE 2.—*Blood Wassermann After Therapy*

Number of Courses	0-1	1-2	2-3	3-4	4-5	5-6	6 Plus
Age Group 0 to 2 Years							
Number patients	1	7	2	.....	.....	1	.....
Per cent negative	100	87	100	.....	.....	100	.....
Per cent less positive	.....	13	.....	.....	.....	.....	.....
Per cent unchanged	.....	....	.....	.....	.....	.....	.....
2 to 5 Years							
Number patients	2	4	2	1	1	.....	.....
Per cent negative	100	100	100	.....	100	.....	.....
Per cent less positive	.....	.....	.....	.....	.....	.....	.....
Per cent unchanged	.....	.....	.....	100	.....	.....	.....
5 to 14 Years							
Number patients	2	23	7	1	1	1	3
Per cent negative	50	50	72	100	.....	100	33
Per cent less positive	....	29	14	.....	100	.....	33
Per cent unchanged	50	21	14	.....	.....	.....	33

symptoms have progressed in only five of the forty-three patients, and only one of the five had much therapy (twenty-nine injections in nine months). There is no instance in twenty-four cases, with known freedom of the nervous system before treatment, in which they developed positive changes.

On the whole, Bismarsen is very helpful, since it penetrates the nervous system better than the other arsphenamins including tryparsamid (Raiziss).

COMPARISON WITH OTHER DRUGS

For two years prior to starting Bismarsen in our Luetic Clinic, only 14 per cent of twenty-seven patients, who had received various drugs, had attained negative serology. This is in marked contrast to 61 per cent of sixty-one patients who have received the present drug since 1930. Part of this difference, however, may be attributed to a more efficient follow-up in vogue at present.

Jeans and Cooke,[4] who used mercuric chlorid and a little sulpharsphenamin for infants for six months' or more treatment, reported that 72 per cent were serologically negative for at least three years. Jeans and Cooke added bismuth intramuscularly for children over one year of age. They reported 12 per cent of cures of those under treatment more than six months and less than one year, and 44 per cent cures of those treated more than one year. Comparatively, Bismarsen figures are about 50 and 43 per cent, respectively, slightly superior.

Stokes,[5] while considering that arsphenamin brings about quicker transformations than neoarsphenamin, has stated that Bismarsen is equal to or better than arsphenamin with bismuth or mercury. He remarked recently that it "has appealed to us as a moderately effective but not particularly impressive agent for the treatment of active tardive prenatal syphilis. It reverses approximately half the apparently fixed positive serological cases, but in interstitial keratitis is too slow, and is comparatively ineffective in prenatal neurosyphilis." I would agree as to the eye condition and the neurosyphilis, but the results in this study of non-neurosyphilitics, largely (70 per cent), show that from 61 per cent to 85 per cent have had a serological blood cure. Chambers and Koetter have reported excellent results with Bismarsen. Sixty-five of one hundred patients had complete Wassermann reversals after three courses of treatment. Only 3 per cent of these patients had serological relapse twenty months after the last treatment; 2 per cent after sixteen months, and 2 per cent after twelve months. Chambers and Koetter attained complete serological reversal in Wassermann-fast cases in 51 per cent of these, and only 8 per cent of them showed ultimate relapse. If sustained, this is a truly remarkable record. Wright,[6] an authority and leading exponent of the use of bismuth, reported 74 per cent reversals of blood serology by the use of bismuth only, 56 per cent reversals by the use of neoarsphenamin or sulpharsphenamin with bismuth. These figures include 150 children enrolled during a ten-year period. Again Bismarsen is somewhat more effective.

RELAPSES

Clinical.—Relapses have been few in number, and are known to have occurred in about ten of 170 patients, mainly in infants with florid secondary lues, which are notoriously difficult to control or cure. Three of this group were neurosyphilitics approaching puberty, another trying problem. Only one case of keratitis relapsed.

Serological.—There was known recurrence in only eight of 170 patients. In one infant the blood remained negative during therapy from the age of seven months to three years, when it again became positive, despite continuous treatment. Two other infants relapsed six months after one course from negative to three plus, but they finally became negative.

Most of the sixty-one patients who had reliable follow-ups have had negative serology from one and a half to five years after the cessation of therapy. We have been unable to follow all of the 170 patients who started therapy. It is possible that even during faithful therapy more clinical and serological relapses would have occurred. The incidence is probably no greater, at the least, than occurs with the other arsenicals, or bismuth alone, or both. However, conversely, an even greater recurrence has probably happened in those patients who have ceased Bismarsen therapy and disappeared.

SUMMARY

1. Bismuth arsphenamin sulfonate (Bismarsen), for the treatment of lues in children, has the great advantage of ease of intramuscular administration. This insures a more constant and prolonged period of therapy, so necessary for congenital lues.

2. Reactions are less common than with the usual antisyphilitic drugs; these occurred in about 0.8 per cent of injections; the local reactions are very mild; the general reactions are more common, usually nitritoid and not often severe.

3. Toxicity is rare. Purpura was the common toxic manifestation.

4. Lesions, especially those in infants, heal promptly. Interstitial keratitis, however, is the slowest lesion to respond.

5. Over 3,200 injections have been given to 170 children during four and a half years.

6. Adequate check on sixty-one patients shows that 61 per cent have a negative blood serology, and 24 per cent show marked attenuation, a total of 85 per cent helped.

7. Patients with neurosyphilis were definitely improved, and further complications probably prevented.

8. Our experience, and that of others who have used various antisyphilitic drugs, indicate that bismarsen is superior for congenital luetics.

9. Clinical relapse occurred in less than 1 per cent of the patients and known serological recurrence in less than 0.5 per cent, although it is apparently too early for final figures.

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DISCUSSION

HARTZELL H. RAY, M. D. (23 Third Avenue, San Mateo).—Doctor Reilly is to be complimented for giving bismarsen a five-year trial before reporting on it. Antisyphilitic remedies need many years of study and wide use to determine their true value. In this study of the use of bismarsen in congenital lues its advantages appear to be ease of administration, low toxicity, equal or better than average serological reversals of Wassermann, and early clinical recovery from symptoms of acute lues. Because of the ease of administration and better attendance of the patient, a more complete course of therapy may be given. This may account in part for the more favorable results obtained. The low toxicity may possibly be due to the fact that this drug contains only a small amount of arsphenamin per dose. Bismarsen, similar to most antisyphilitic remedies used in congenital lues, seems to give the best serological results when used in children before the age of two years, and when given fairly regularly over a period of time. Bismarsen, in ages over two years, seems to give a little better than average serological result. Because of its evident advantages, bismarsen is a drug that should receive a more widespread clinical trial.

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MERLIN T.-R. MAYNARD, M. D. (Medico-Dental Building, San Jose).—Doctor Reilly has covered the use of bismarsen in the treatment of congenital luetics very completely. I feel that whatever comment I can make will be simply that of emphasis.

I would question, however, his statement that bismarsen is less toxic than neoarsphenamin. I believe that if equivalent therapeutic dosage be given, we will consistently find that arsphenamins containing sulphur in their compound are distinctly more likely to produce constitutional reactions and damage. Nitritoid reactions occur quite commonly, and purpuric reactions are also definitely more frequent.

Something should also be said for preliminary iodid therapy. I believe the intravenous administration of sodium iodid to be a very valuable preliminary to all arsenical therapy, particularly in those cases in which the liver is large and liver function is distinctly damaged. I further believe that the giving of liver extract is also worth while in connection with the bismarsen therapy.

The great group of luetic children are treated by the family physician, where the ease of administration of bismarsen and the good results in treatment outweigh the danger of reactions. I want to emphasize that the attention of the general practitioner must be directed toward these complications as much as toward its therapeutic benefits.

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STANLEY O. CHAMBERS, M. D. (1260 Roosevelt Building, Los Angeles).—Bismarsen is a drug proved of value in the treatment of syphilis, and particularly adapted to the infant and child. Its simplicity of administration and apparent therapeutic effectiveness emphasize that adaptability.

Doctor Reilly has treated and observed a very well-controlled group in the congenital class, and his results merit careful and thorough consideration. It is true that there were evidences noted in our original group of a tendency for the drug to act more slowly than other of the arsphenamin derivatives. This fact may, however, be an advantage rather than a disadvantage when we consider the desirability of slow healing where vital tissues are involved.

We already appreciate the need for utilizing this principle in hepatic syphilis. When we eliminate this questionable point from the list of therapeutic effects, bismarsen appears to equal if not exceed the value of other drugs commonly used in the treatment of the congenital syphilitic. Its almost negligible incidence of untoward reactions and its great simplicity of administration certainly should warrant its place in the therapeutic armamentaria if the record of effectiveness can be sustained.

THE LURE OF MEDICAL HISTORY†

DISEASES OF THE INDIANS OF LOWER CALIFORNIA IN THE EIGHTEENTH CENTURY*

By S. F. COOK, Ph.D.
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Foreword.—A translation of a chapter from: Descripción breve de la California, su situación, extensión, costas, etc. Con otras noticias que pueden conducir para el conocimiento de ellas. El autor de esta descripción fué un Misionero Jesuita de la California. (Probably about 1770.)

Translator's Note.—There is no doubt that the following short treatise represents one of the earliest attempts by a contemporary observer to discuss, in a comprehensive fashion, the diseases to which the Pacific Coast Indians were subject after the advent of the white man. The author does not attempt to consider at length the native maladies and the native cures, but limits himself primarily to syphilis and the epidemic plagues which were observed in Lower California. Although he writes anonymously, the author states that he was a Jesuit missionary in this region for many years and, therefore, his statements may be considered as first-hand evidence. The original document, from which this excerpt is taken, is in the Biblioteca Capitular Columbina in Seville, Spain; and a transcript is in the Bancroft Library at the University of California, Berkeley.

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IT is an unquestionable fact that the climate of this section of California is well suited to foreigners, and much more so to the native Indians. These natives are, commonly, of a very ruddy complexion and of a hot-blooded nature. They have a cooling fruit, which helps to relieve this condition. To my sight, the cause of their robustness is the frugal way of living which they, of necessity, must endure. Although the races, fights, and other exertions in which they indulge occasionally give them injuries of the chest, it is also certain that, through them, they lay aside their

† A Twenty-Five Years Ago column, made up of excerpts from the official journal of the California Medical Association of twenty-five years ago, is printed in each issue of CALIFORNIA AND WESTERN MEDICINE. The column is one of the regular features of the Miscellany department, and its page number will be found on the front cover.

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